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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,982	05/02/2006	Makoto Koizumi	06189/HG	2978
1933 7590 04/29/2009 FRISHAUF, HOLTZ, GOODMAN & CHICK, PC 220 Fifth Avenue 16TH Floor NEW YORK, NY 10001-7708				
EXAMINER				
STAPLES, MARK				
ART UNIT		PAPER NUMBER		
1637				
MAIL DATE		DELIVERY MODE		
04/29/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/577,982

Applicant(s)

KOIZUMI, MAKOTO

Examiner

MARK STAPLES

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 8-54 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 and 44-51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 12-43 and 52-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/06)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/02/2009 has been entered.

2. Claims 1-5, 12-43, and 52-54 filed on 04/23/2008 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration Sufficient to Overcome Claim Rejections

3. The Declaration under 37 CFR 1.132 filed 02/02/2009 is sufficient to overcome the rejection of claims 1-5, 12-43, and 52-54 based upon Latorra et al. (2003) under 35 U.S.C. 103(a).

Applicant's evidence and analysis provided in the Declaration are sufficient to support the position that Latorra et al. only teach LNA substitutions at the first position of the 3' end of primers and thus the teachings of Latorra et al. do not make obvious the instant claims which recite an oligonucleotide comprising an ENA unit which is the third position from the 3' end of oligonucleotides. In the prior claim rejections, Latorra et al.

was relied upon for teaching the third position and Koizumi et al. (2003) was relied upon for substitution of ENA units for LNA units. Furthermore, none of the teachings of other cited references of Koizumi et al. (2003), Weston et al. (2002), and Stanton et al. (2001) alone or in combination make obvious the instant claims. Based upon the cited prior art of Latorra et al., an oligonucleotide comprising an ENA unit which is the third position from the 3' end of oligonucleotides would not have been obvious to one of ordinary skill in the art.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

4. The rejection of claims 1-5, 23, 29, and 41 under 35 U.S.C. 103(a) as being unpatentable over Latorra et al. (06/04/2003) and Koizumi et al. (2003) is withdrawn. Applicant's argument in the Declaration is found persuasive to overcome the rejection of the claims based upon Latorra et al.
5. The rejection of claims 12-19 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Latorra et al., Koizumi et al. , and Weston et al. (2002) is withdrawn. Applicant's argument in the Declaration is found persuasive to overcome the rejection of the claims based upon Latorra et al.
6. The rejection of claims 20-22, 24-28, 30-40, and 42-43 under 35 U.S.C. 103(a) as being unpatentable over Latorra et al. and Koizumi et al., and further in view of Stanton et al. (2001) is withdrawn. Applicant's argument in the Declaration is found persuasive to overcome the rejection of the claims based upon Latorra et al.

New Rejections

Claim Rejections - 35 USC § 112 First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims recite an oligonucleotide, comprising nucleotides complementary to a reference nucleotide of a target gene. This large genus of target genes is represented in the specification by the target genes: HLA, TCRalpha, APOE4, tryptophan hydroxylase, leptin, human prothrombin, cytochrome P4501A2, cytochrome P4502A6, cytochrome P4502C9, cytochrome P4502C19, cytochrome P4502D6, cytochrome P4502E1, thiopurine methyltransferase, N-acetyltransferase, UDP-glucuronosyltransferase, glutathione S-transferase. Thus, applicant has expressed possession of only a few species in a genus, which comprises hundreds of millions of different possibilities considering the genes within an individual and the genes across species and genera. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in

possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the target genes are disclosed. With regard to the various genes across individuals, species, and genera, this is insufficient to demonstrate identity of all target genes of the claimed invention. Instant claims are overly broad in the recitation of "comprising" since no guidance is provided as to which of the variant oligonucleotides would comprise a nucleotide complementary to the reference nucleotide of a target gene. Further no information is given in the specification regarding a methodology to determine such common elements or attributes.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

It is noted that in *Fiers v. Revel* (25 USPQ2d, 1601), the Fed. Cir. concluded that "when an inventor is unable to envision the detailed chemical structure of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred".

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of various target genes and no correlative structure claimed product.

Accordingly, the specification does not provide a written description of the invention of claims 1-4 and 12-17.

9. Claims 23, 29, 35, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims recite an oligonucleotide, comprising nucleotides complementary to a reference nucleotide of a target gene where the target gene is a disease causing gene or a disease associated gene. This large genus of disease causing genes and disease associated genes is represented in the specification by the genes: HLA, TCRalpha, APOE4, ryptophan hydroxylase, leptin, human prothrombin, and blood coagulation factor VII. Thus, applicant has expressed possession of only a few species in a genus, which comprises hundreds of millions of different possibilities considering the genes within an individual and the genes across species and genera.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the target genes are disclosed. With regard to the various genes across individuals, species, and genera, this is insufficient to demonstrate identity of all target genes of the claimed invention. Instant claims are overly broad in the recitation of " comprising" since no guidance is provided as to which of the variant oligonucleotides would comprise a nucleotide complementary to the reference nucleotide of a target disease causing gene or a disease associated gene. Further no information is given in the specification regarding a methodology to determine such common elements or attributes.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious,"

and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

It is noted that in *Fiers v. Revel* (25 USPQ2d, 1601), the Fed. Cir. concluded that "when an inventor is unable to envision the detailed chemical structure of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred".

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of various target disease causing genes or target disease associated genes and no correlative structure claimed product.

Accordingly, the specification does not provide a written description of the invention of claims 23, 29, 35, and 41.

10. Claims 24, 30, 36, and 42, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The target gene is selected from the group consisting of a causative gene of ulcerative colitis, a causative gene of arthritis rheumatoides, a causative gene of Alzheimer's disease, a causative gene of schizophrenia, a causative gene of manic-depressive psychosis, a causative gene of albuminuria, a causative gene of myocardial infarction and a causative gene of adiposis.

The current claims recite an oligonucleotide, comprising nucleotides complementary to a reference nucleotide of a target gene where the target gene is a causative gene of: ulcerative colitis, arthritis rheumatoides, Alzheimer's disease, schizophrenia, manic-depressive psychosis, albuminuria, myocardial infarction or adiposis. This large genus of disease causing genes and disease associated genes is represented in the specification by no causative genes of: ulcerative colitis, arthritis rheumatoides, Alzheimer's disease, schizophrenia, manic-depressive psychosis, albuminuria, myocardial infarction or adiposis. Thus, applicant has expressed possession of no species in a genus, which comprises hundreds of millions of different possibilities considering the genes within an individual and the genes across species and genera. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the target genes are disclosed. With regard to the various genes across individuals, species, and genera, this is insufficient to demonstrate identity of all target genes of the claimed invention. Instant claims are overly broad in the recitation of "comprising" since no guidance is provided as to which of the variant oligonucleotides would comprise a nucleotide complementary to the reference nucleotide of a target causative gene. Further no information is given in

the specification regarding a methodology to determine such common elements or attributes.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

It is noted that in *Fiers v. Revel* (25 USPQ2d, 1601), the Fed. Cir. concluded that "when an inventor is unable to envision the detailed chemical structure of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred".

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of various target causative genes and no correlative structure claimed product.

Accordingly, the specification does not provide a written description of the invention of claims 24, 30, 36, and 42.

11. Claims 25, 29, 37, and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims recite an oligonucleotide comprising nucleotides complementary to a reference nucleotide of a target gene where the target gene is a dopamine D3 receptor or an angiotensin precursor. This large genus of disease causing genes and disease associated genes is not supported in the specification by a single gene. Thus, applicant has expressed possession of no species in a genus, which comprises hundreds of millions of different possibilities considering the genes within an individual and the genes across species and genera. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the target genes are disclosed. With regard to the various genes across individuals, species, and genera, this is insufficient to demonstrate identity of all target genes of the claimed invention. Instant claims are overly broad in the recitation of " comprising" since no guidance is provided as to which of the variant oligonucleotides would comprise a

nucleotide complementary to the reference nucleotide of a target dopamine D3 receptor or target angiotensin precursor genes. Further no information is given in the specification regarding a methodology to determine such common elements or attributes.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

It is noted that in *Fiers v. Revel* (25 USPQ2d, 1601), the Fed. Cir. concluded that "when an inventor is unable to envision the detailed chemical structure of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred".

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of various target dopamine D3

receptor or target angiotensin precursor genes and no correlative structure claimed product.

Accordingly, the specification does not provide a written description of the invention of claims 25, 29, 37, and 43.

12. Claims 26, 32, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims recite an oligonucleotide comprising nucleotides complementary to a reference nucleotide of a target gene where the target gene is a drug metabolizing gene. This large genus of drug metabolizing genes is represented in the specification by cytochrome P4501A2, cytochrome P4502A6, cytochrome P4502C9, cytochrome P4502C19, cytochrome P4502D6, and cytochrome P4502E1 genes. Thus, applicant has expressed possession of six species in a genus, which comprises hundreds of millions of different possibilities considering the genes within an individual and the genes across species and genera. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed."

(See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the target genes are disclosed. With regard to the various genes across individuals, species, and genera, this is insufficient to demonstrate identity of all target drug metabolizing genes of the claimed invention. Instant claims are overly broad in the recitation of "comprising" since no guidance is provided as to which of the variant oligonucleotides would comprise a nucleotide complementary to the reference nucleotide of a target drug metabolizing genes. Further no information is given in the specification regarding a methodology to determine such common elements or attributes.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

It is noted that in *Fiers v. Revel* (25 USPQ2d, 1601), the Fed. Cir. concluded that "when an inventor is unable to envision the detailed chemical structure of the gene so

as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred”.

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of various target drug metabolizing genes and no correlative structure claimed product.

Accordingly, the specification does not provide a written description of the invention of claims 25, 29, 37, and 43.

New Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 1-5, 23, 29, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morita et al (Jan. 2002, cited on the IDS), Braasch et al. (2001), and Orum et al. (1999, noting this is reference no. 29 of Braasch et al.).

Regarding claims 1, 2, 5, 23, and 29, Morita et al. (2002) teach oligonucleotides comprising:

(a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first

nucleotide, and the other nucleotides are natural nucleotides (entire article, especially the last Figure 1 where X is the ENA unit designated as eT);

(b) a nucleotide complementary to the reference nucleotide of a target at the 3'-end position thereof (see the Table 1); and having

(c) nucleotides complementary to a nucleotide sequence of the target in other positions (see the Table 1).

It is noted that elements (b) and (c) are "intended uses" and carry no patentable weight. However, Morita et al. teach certain of these elements as noted above.

Regarding claims 1, 2, 5, 23, and 29, Morita et al. (2001) do not specifically teach an ENA unit at the third position from the 3' end; do not specifically teach the "intended use" of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide. Morita et al. suggest but do not specifically teach for a single oligonucleotide, both a sole ENA at the second position from the 3' end and the "intended use" of the nucleotides being complementary. Morita et al. teach these "intended uses" for two separate oligonucleotides as given respectively in Figure 1 and Table 1.

Regarding claims 1, 2, 5, 23, and 29, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

(a) 2'-O,4'-C-methylene nucleotide (LNA) units (see Figure 1) which can be the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is

defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Table 1 of Orum et al.); and

(b) a nucleotide complementary to the reference nucleotide of a target gene of Factor V at the 3'-end position thereof (see Table 3 for various position, especially the first three oligonucleotides and entries 9-12 from the bottom) which can be the mutant nucleotide, the mutation of the Factor V gene (see 3rd paragraph on p. 6), and

(c) nucleotides complementary to the nucleotide sequence of the target genes of the disease causing Factor V gene (where individuals see 3rd paragraph on p. 6, see Abstract for the general teaching of LNA substituted oligonucleotides which are complementary to genes, and as evidenced in the last sentence on p. 1898 of Orum et al.).

Regarding claims 3-5 and 41, Braasch et al. teach oligonucleotides of 18 to 25 bases (see Table 3) comprising:

(a) a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the reference/wild type nucleotide of a target gene and teach a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the mutant nucleotide of a target gene (see Table 3 especially 9th and as evidenced throughout Orum et al., especially Table 1),

(b) wherein a nucleotide which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and wherein the second nucleotide of each oligonucleotide of claims 3 and 4 is a

nucleotide that is not complementary respectively to the nucleotide of a reference/wild type gene and the mutant gene (see Table 1 of Orum et al.).

(c) nucleotides complementary to the nucleotides of the target gene at other positions; and

(d) a nucleotide which is the fourth or fifth nucleotide from the 3'-end of each oligonucleotide is an LNA unit (see Table 1 of Orum et al.).

Regarding claims 1-5, Braasch et al. and Orum et al. teach multiple and various positions and arrangements of LNA units but do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit, and do not specifically teach all of the limitations and intended uses of the claimed oligonucleotide in a single oligonucleotide but with LNA units. Braasch et al. and Orum et al. do teach the limitations and intended uses of the claims but in different oligonucleotides and with LNA units instead of ENA units.

Regarding claims 1-5, Morita et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Morita et al. further teach that substitution of ENA units for LNA units leads to improved properties of oligonucleotides, including: *fi*) having a high binding affinity for complementary RNA and *fi*) being more nuclease-resistant than natural DNA and BNA/LNA (see Abstract).

Regarding claims 1-5, Morita et al. teach an oligonucleotide comprising an ENA unit at the second position from the 3' end, but do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Braasch et al. and Orum et al. teach several oligonucleotides comprising LNA units at the third position from the 3' of an oligonucleotide. Braasch et al. and Orum et al. do not specifically teach ENA units. Morita et al. teach that oligonucleotides can comprise either LNA units or ENA units. Furthermore Morita et al. teach that substitution of ENA units for LNA units in a oligonucleotide results in improved properties of that nucleotide. Because both Braasch et al. and Orum et al. because Morita et al. all teach oligonucleotides comprising LNA units, it would have been obvious to one skilled in the art to substitute an ENA unit as taught by Morita et al. for the LNA unit as taught by Braasch et al. and Orum et al. in order to achieve the predictable result of an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Furthermore, Braasch et al. and Orum et al. teach that LNA are a valuable tool kit for nucleic acid recognition and chemical genetics (see last sentence). Morita et al. additionally teach the use of ENA units can be further optimized including for improved nuclease resistance (see last paragraph). Thus, it would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to place an ENA at third position from the 3' end of oligonucleotides as disclosed by Applicant instead of the second position as used by Morita et al. since these differences in

position would not be expected to greatly alter the properties of the oligonucleotides. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the position of the ENA unit could be adjusted to maximize the desired results, as each of Braasch et al. and Orum et al. disclose general and varied positions for LNA units including the third position and Morita et al. also disclose varying positions for ENA units and that substitution of ENA units of LNA units is desirable owing to the improved properties of ENA units in oligonucleotides. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the third position for the ENA unit over the second position was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art, especially in regards to the properties of ENA units. As noted, a skilled artisan would expect an ENA unit at the third position to have nearly identical properties of ENA units as the second position for oligonucleotides. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

15. Claims 12-19 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morita et al (Jan. 2002, cited on the IDS), Braasch et al. (2001), Orum et al. (1999, noting this is reference no. 29 of Braasch et al.), and Weston et al. (U.S. Patent No. 6,391,593 issued 2002, previously cited).

Regarding claims 12-18, Morita et al. (2002) teach oligonucleotides comprising:

- (a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (entire article, especially the last Figure 1 where X is the ENA unit designated as eT);
- (b) a nucleotide complementary to the reference nucleotide of a target at the 3'-end position thereof (see the Table 1); and having
- (c) nucleotides complementary to a nucleotide sequence of the target in other positions (see the Table 1).

It is noted that elements (b) and (c) are "intended uses" and carry no patentable weight. However, Morita et al. teach certain of these elements as noted above.

Regarding claims 12-18, Morita et al. (2001) do not specifically teach an ENA unit at the third position from the 3' end; do not specifically teach the intended use of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide. Morita et al. suggest but do not specifically teach for a single oligonucleotide, both a sole ENA at the second position from the 3' end and the "intended use" of the nucleotides being complementary. Morita et al. teach these

"intended uses" for two separate oligonucleotides as given respectively in Figure 1 and Table 1.

Regarding claims 12-18, Morita et al. do not specifically teach a kit.

Regarding claims 12, 13, 19, and 52, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

(a) 2'-O,4'-C-methylene nucleotide (LNA) units (see Figure 1) which can be the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Table 1 of Orum et al.); and

- (b) a nucleotide complementary to the reference nucleotide of a target gene of Factor V at the 3'-end position thereof (see Table 3 for various position, especially the first three oligonucleotides and entries 9-12 from the bottom) which can be the mutant nucleotide, the mutation of the Factor V gene (see 3rd paragraph on p. 6), and
- (c) nucleotides complementary to the nucleotide sequence of the target genes of the disease causing Factor V gene (where individuals see 3rd paragraph on p. 6, see Abstract for the general teaching of LNA substituted oligonucleotides which are complementary to genes, and as evidenced in the last sentence on p. 1898 of Orum et al.).
- (b) a second oligonucleotide which is a reverse primer (see 4th paragraph on p. 1900 of Orum et al.),
- (c) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and
- (d) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 14, 18, 19, and 53, Braasch et al. teach oligonucleotides of 18 to 25 bases (see Table 3) comprising:

- (a) a first oligonucleotide which is a primer/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Table 3 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900), the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900), wherein the forward primer/probe can be one

which is either complementary to the reference/wild type gene or the mutant gene (see last entry in Table 1 and see Orum et al.) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Favtor V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7); and

- (b) a second oligonucleotide which is forward primer 2/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);
- (c) a third oligonucleotide which is reverse primer 1/probe capable of amplifying a sequence of interest together with the forward primer 1/probe (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900),
- (d) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and
- (e) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 15, 16, 18, 19, and 54, Braasch et al. teach an oligonucleotides of 18 to 25 bases (see Table 3) comprising:

- (a) a first oligonucleotide which is a forward primer/probe having
 - (i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last

sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Favior V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7).;

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(b) a second oligonucleotide which is one of the reverse primers/probe capable of amplifying a sequence of interest together with the forward primers (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(c) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and

(d) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 17-19 and 54, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

((a) a first oligonucleotide which is a forward primer/probe having

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Factor V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7).;

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(b) a second oligonucleotide having a

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

- (ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);
- (iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and
- (ii) forward primer 3/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);
- (c) a third oligonucleotide which is any one of the respective reverse primers capable of amplifying a sequence of interest together with the forward primer (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);
- (d) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and
- (e) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 12-18, Orum et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit and do not specifically teach a kit. Braasch et al. teach a general kit (see last sentence) but do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit.

Regarding claims 12-18, Morita et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Morita et al. further teach that substitution of ENA units for LNA units leads to improved properties of oligonucleotides, including: *(i)* having a high binding affinity for complementary RNA and *(ii)* being more nuclease-resistant than natural DNA and BNA/LNA (see Abstract).

Regarding claims 1-5, Morita et al. teach an oligonucleotide comprising an ENA unit at the second position from the 3' end, but do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Braasch et al. and Orum et al. teach several oligonucleotides comprising LNA units at the third position from the 3' of an oligonucleotide. Braasch et al. and Orum et al. do not specifically teach ENA units. Morita et al. teach that oligonucleotides can comprise either LNA units or ENA units. Furthermore Morita et al. teach that substitution of ENA units for LNA units in an oligonucleotide results in improved properties of that nucleotide. Because both Braasch et al. and Orum et al. because Morita et al. all teach oligonucleotides comprising LNA units, it would have been obvious to one skilled in the art to substitute an ENA unit as taught by Morita et al. for the LNA unit as taught by Braasch et al. and Orum et al. in order to achieve the predictable result of an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Furthermore, Braasch et al. and Orum et al. teach that LNA are a valuable tool kit for nucleic acid recognition and chemical genetics (see last sentence). Morita et al. additionally teach the use of ENA units can be further optimized including for improved nuclease resistance (see last paragraph). Thus, it would also have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place an ENA at third position from the 3' end of oligonucleotides as disclosed by Applicant instead of the second position as used by Morita et al. since these differences in position would not be expected to greatly alter the properties of the oligonucleotides. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the position of the ENA unit could be adjusted to maximize the desired results, as each of Braasch et al. and Orum et al. disclose general and varied positions for LNA units including the third position and Morita et al. also disclose varying positions for ENA units and that substitution of ENA units of LNA units is desirable owing to the improved properties of ENA units in oligonucleotides. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the third position for the ENA unit over the second

position was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art, especially in regards to the properties of ENA units. As noted, a skilled artisan would expect an ENA unit at the third position to have nearly identical properties of ENA units in the second position for oligonucleotides. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

Regarding claims 12-18, Weston et al. teach kits comprising oligonucleotides with LNA units, DNA polymerases, and PCR buffers (see column 7 lines 41-51 and see claims 20 and 21).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Morita et al., Braasch et al., and Orum et al. by incorporating them in a kit as suggested by Weston et al. with a reasonable expectation of success. The motivation to do so is provided by Weston et al. who teach the convenience and advantage of kits comprising oligonucleotides, DNA polymerase, and PCR buffers (see column 7 lines 41-51). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

16. Claims 20-22, 24-28, 30-40, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morita et al., Braasch et al., and Orum et al. as applied to claims 1-4 above, and further in view of Stanton et al. (US publication No. 20010034023 published 2001 and previously cited).

Morita et al., Braasch et al., and Orum et al. teach as noted above.

Morita et al., Braasch et al., and Orum et al. do not teach the limitations of claims 20-22, 24-28, 30-40, and 42-43.

Regarding claims 20-22, 24-28, 30-40, and 42-43 Stanton et al. teach oligonucleotides/primers for detecting drug metabolizing genes (entire publication, especially paragraph 0143) which are glutathione transferase, N-acetyltransferase (see paragraph 0262), Human cytochrome P4502C9 (see Table 2121 at paragraph 1058)) which are associated with Alzheimer's disease (see paragraph 0023) and teach the target gene which is HLA (see paragraph 0760).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Morita et al., Braasch et al., and Orum et al. by making oligonucleotides to detect drug metabolizing genes as suggested by Stanton et al. with a reasonable expectation of success. The motivation to do so is provided by Stanton et al. who teach that such oligonucleotides can be used in methods: "... for identifying and utilizing variances in genes relating to efficacy and safety of medical therapy and other aspects of medical therapy" (see Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

17. No claim is free of the prior art
18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Mark Staples

/M. S./

Examiner, Art Unit 1637

April 27, 2009

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637